In Vitro and In Vivo Assessment of Regional Nasal Deposition using Scintigraphy from a Nasal Spray and a Nasal Powder

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SUMMARY

Case studies which utilized scintigraphy to link in vitro and in vivo nasal spray deposition from a nasal spray and a powder were undertaken. In vitro deposition in a nasal cast illustrated that significantly higher deposition (p<0.05) was observed in the olfactory region for the unit-dose powder device compared to the multi-dose liquid nasal spray pump. In vivo studies in healthy volunteers also demonstrated increased deposition in the olfactory region for the nasal powder compared to the nasal spray.

Coupling in vitro and in vivo nasal deposition has the potential to provide valuable insight into the utility of in vitro studies to inform subsequent clinical studies during the development of nasal drug delivery therapies, whether they be local or systemic.

INTRODUCTION

Nasal drug delivery offers significant opportunities for introducing new therapies, whether they be local, systemic or via the nose-to-brain pathway [1]. Predicting the nasal deposition of new drug candidates in order to facilitate the development pathway is essential for both liquid
and powder formulations. It is important to understand regional nasal deposition as it may be necessary to target different areas in the nasal cavity, e.g., the olfactory region for central nervous system (CNS) therapies. Linking in vitro development work and in vivo studies can potentially streamline the development process. Historically nasal casts have been used to create in vitro nasal deposition data, but these models are known to have limitations or have not been directly correlated to in vivo deposition [2, 3], thus limiting their usefulness. This article describes case studies which utilize validated scintigraphy techniques to link in vitro and in vivo nasal spray deposition from a nasal spray and a powder which could predict subsequent nasal therapy uptake to facilitate the development of nasal drug delivery therapies.

MATERIALS AND METHODS

Nasal delivery devices and formulations

Two different nasal devices and formulations were used to investigate deposition profiles. A multi-dose liquid spray pump (Figure 1A, VP7, Aptar Pharma, France), was used to deliver 50 µL of radiolabelled saline solution per nostril. The radiolabel was Diethylene Triamine Penta acetic Acid – Technicium (DTPA-Tc⁹⁹m) and one 50 µL dose of the radiolabelled solution had a radioactive content of ~1.5 MBq (megabecquerel). The droplet size distribution was measured by laser diffraction (Spraytec, Malvern Panalytical, UK) following the validated labeling procedure [4] and characterized as Dv10 = 19 µm, Dv50 = 39 µm, and Dv90 = 83 µm, respectively.

A unit dose powder device (Figure 1B, UDS powder, Aptar Pharma, France) was used to deliver 10 mg of radiolabelled lactose powder (Respitose®, DFE Pharma, Germany) per nostril. Lactose was radiolabelled with DTPA-Tc⁹⁹m using a validated labelling procedure [4] in order to deliver ~10 mg of powder per dose with a radioactive content of ~1.5 MBq. The lactose particle size distribution was measured by laser diffraction (Spraytec, Malvern Panalytical, UK) following the validated labelling procedure and characterized as Dv10 = 31 µm, Dv50 = 80 µm, and Dv90 = 190 µm, respectively.

Figure 1. Multi-dose liquid spray pump (A) and unit-dose powder device (B).

In vitro and in vivo deposition imaging

In vitro deposition of the nasal spray and nasal powder were characterized in a nasal cast using scintigraphy. The nasal cast model was manufactured from epoxy plastic based on Computed Tomography (CT)-scans of a plastinated head model [5], previously validated as a predictive model for nasal aerosol deposition [6]. Figure 2 shows the four parts of the nasal cavity from the nose to the nasopharynx, allowing the in-situ assay of deposited particles in each region of interest. The
The nose component was made from silicone to represent the flexibility of the human nostril. Based on Buck et al. [7], approximately one third of the upper part of the nasal cavity, between the nose/nasal valve and the rhinopharynx, was considered to be the area that defines the olfactory epithelium, which is often targeted for the nose-to-brain drug delivery pathway.

In vivo deposition imaging was also conducted with six healthy volunteers using the same liquid and powder nasal devices described above, see Figure 1. The liquid and powder formulations were radiolabeled using the same validated procedure that was used in the in vitro study [4].

**RESULTS AND DISCUSSION**

Table 1 compares % deposition in the nasal cast for the nasal spray and the UDS powder device. The radiolabelled images revealed a notable difference between the liquid nasal spray and the UDS powder device in terms of radioactive deposition within the nasal cast. Higher deposition was observed in the olfactory region for the UDS powder device compared to the liquid nasal spray pump.

<table>
<thead>
<tr>
<th>Regions of interest</th>
<th>Deposition % +/- SD</th>
<th>Deposition % +/-SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nose*</td>
<td>51 ± 6</td>
<td>14 ± 4</td>
</tr>
<tr>
<td>Lower zone*</td>
<td>13 ± 5</td>
<td>8 ± 3</td>
</tr>
<tr>
<td>Middle zone</td>
<td>30 ± 2</td>
<td>37 ± 4</td>
</tr>
<tr>
<td>Olfactory zone*</td>
<td>6 ± 3</td>
<td>34 ± 7</td>
</tr>
<tr>
<td>Rhinopharynx*</td>
<td>1 ± 0</td>
<td>6 ± 3</td>
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</table>
Figure 3 compares typical images from the in vitro and in vivo nasal spray deposition studies. Fiducial markers are the two upper scintigraphy markers visible in Figures 3C and 3D. Stronger scintigraphy signals were noted in the interior and upper parts of the nasal cavity for the powder device whereas more holdup in the nose area was noted for the liquid device.

The radiolabeled images similarly revealed significant (p<0.05) differences between the liquid nasal spray and the UDS powder device in terms of radioactive deposition in the nose, lower and olfactory zones. Not surprisingly, increased variability was observed in vivo because the volunteers have differing nasal anatomies; in vitro studies used a single anatomical model. The liquid nasal spray showed increased deposition in the nose possibly due to a wider spray angle than the powder device (liquid spray angle ~40°, powder spray angle ~20°). More material is able to reach the internal areas of the nasal cavity from the powder device and subsequently increased deposition is observed including the olfactory region (~4 ± 3.8% (liquid) vs ~20 ± 9% (powder)).

Both the in vitro and in vivo studies confirm the same trends with regard to deposition in the nasal cavity from the liquid and powder nasal spray devices. However, correlation of in vitro and in vivo nasal deposition still remains a challenge due to multiple factors [3]. In vitro nasal casts are made from rigid (usually plastic) materials and the internal surfaces do not closely resemble the humid mucosal environment found in the human nasal cavity. This could potentially be mitigated by humidifying and coating the internal surfaces before conducting in vitro testing. Device position in the nostril pre-dosing can also influence subsequent deposition in vitro; the nasal cast used in this work incorporates a flexible silicone nose-piece which more closely resembles the in vivo situation. In vitro nasal cast models are often constructed from 3D files of imaging scans from individuals and can show less variability in deposition studies compared to real and diverse patient populations. One way to address this limitation is to validate so-called ‘idealized casts’ using in vivo deposition studies so that the casts are more representative of patients overall. In addition, different in vitro nasal casts may need to be developed and validated to cover the various patient populations.
that use nasal therapies, e.g., pediatric, geriatric, male, female, etc. Bridging the gap with regards to the potential differences between in vitro and in vivo nasal deposition techniques should improve in vitro-in vivo correlations and bring us closer to useful predictive in vitro nasal deposition tools.

**CONCLUSIONS**

Both in vitro and in vivo scintigraphy studies confirm the same trends with regards to deposition in the nasal cavity. The UDS powder device delivered a higher dose to the olfactory region and less powder to both the nose and lower regions of the nasal cavity, compared to the nasal spray. Unsurprisingly, it was observed that in vitro delivery was less variable than in vivo delivery likely due to the fact that the in vitro model is based on a single anatomy whereas the in vivo work was undertaken with multiple healthy volunteers with differing anatomies.

The outcomes indicate that it is possible to differentiate various nasal spray device parameters including liquid or powder formulations and deposition in nasal regions of interest. Coupling in vitro with in vivo nasal deposition studies could provide valuable insights into how nasal therapies may be deposited and taken up and provide predictive guidance for pre-clinical efficacy studies. Suitably validated nasal cast models may provide predictive in vitro guidance to inform subsequent in vivo deposition during the early development stages of nasal drug delivery therapies.

**REFERENCES**


